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Features and differentiation of dendritic cells in cutaneous lupus erythematosus

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Abstract

In view of the critical role of dendritic cells (DC) in immune mediated skin diseases, we have investigated the differentiation pathways and the possible role of skin DC in the pathogenesis of cutaneous lupus erythematosus (LE). Our immunohistologic and electron-microscopic findings suggest that, in the lesional dermis of cutaneous LE, a delayed-type, CD_4^+ T-cell/CD_{1a}^+ DC immune response is possibly modulated by a suppressor T cell circuit in which CD_{36}^+ DC may act as accessory cells. CD_{11c}^+ and CD_{14}^+ cells with peculiar ultrastructure are possible precursors of both $CD^1{}_a^+$ and CD_{36}^+ DC in the dermis. The altered differentiation and expression of functionally meaningful molecules (HLA-DR) by epidermal Langerhans cells in the lesional skin, related to the epidermal damage putatively (co)provoked by the dermal immune reaction, suggest an impairment of their immunological efficiency.

Introduction

In view of the critical role of dendritic cells (DC) in immune mediated skin diseases [1], we have investigated the differentiation pathways of skin DC and their possible role in the pathogenesis of cutaneous lupus erythematosus (LE) [2,3] lesions. Therefore, we have studied the antigenic profile, number and distribution of DC and their putative precursors in 13 patients with cutaneous LE.

Patients and Methods

We studied 13 patients (six males, seven females; age range 18–51, median 34). Eight patients had chronic discoid LE (CDLE); five patients had subacute cutaneous LE (SCLE). The diagnosis was established according to the clinical, histological, and immunopathological criteria proposed by Sontheimer et al. [2].

Biopsies were taken under local anesthesia from lesional and perilesional skin.

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Each tissue specimen was in part formalin-fixed and paraplast-embedded for routine histological examination, in part snap frozen and stored at –80°C until sectioning and preparation for routine immunofluorescence and immunohistochemistry (alkaline phosphatase antialkaline phosphatase (APAAP) technique) [4]. In six patients (four with CDLE and two with SCLE), part of the biopsy was prepared with routine methods for electron microscopy (EM).

Results

A synthesis of the results is reported below. The quantitative data concerning CD_{1a}, CD_{14}, CD_{36}, and HLA-DR antigen expression by DC are specified in Tables 1 and 2.

The number of CD_{1a}^+ DC in nonatrophic areas of lesional epidermis was similar to that in perilesional skin. In atrophic epidermal areas, on the contrary, the number of CD_{1a}^+ DC was clearly lower, and CD_{11c}^+ and CD_{14}^+ cells – presumable precursors to CD_{1a}^+ DC – were constantly found. The expression of HLA-DR antigen by epidermal DC was reduced throughout the lesional epidermis, as compared with perilesional, clinically normal skin. By EM, epidermal DC appeared poor in organelles and dendrites and contained tubuloreticular inclusions.

Both CD_{1a}^+/HLA-DR$^+$ DC and CD_{36}^+/HLA-DR$^+$ DC, the latter mainly in perivascular location, and in higher numbers as compared to perilesional skin or to

Table 1. Density of cells in the epidermis of 13 cutaneous LE patients (n cells per 100 basal cell nuclei: atrophic/nonatrophic/perilesional epidermis)

		CD_{1a}	HLA-DR	CD_{14}
CDLE	Range	0–4/5–8/6–11	0–1/1–3/5–9	1–4/0–0/0–0
	Mean	2.3/6.8/8.3	0.4/1.8/6.6	2.1/0/0
	±SD	1.16/1.30/1.75	0.52/0.84/1.51	2.13/0/0
SCLE	Range	2–4/6–10/8–11	0–1/2–4/6–10	3–4/0–0/0–0
	Mean	3.0/7.8/9.2	0.5/2.8/7.6	3.5/0/0
	±SD	1.41/1.64/1.30	0.71/1.10/1.52	0.71/0/0

Table 2. Density of cells in the dermis of 13 cutaneous LE patients. (n cells per 100 dermal cell nuclei: lesional/perilesional dermis)

		CD_{1a}	CD_{36}	HLA-DR	CD_{14}
CDLE	Range	16–32/0–2	13–19/5–10	71–83/4-10	6–11/1–4
	Mean	24.3/0.5	15.4/7.4	77.8/7.0	9.0/2.9
	± SD	5.99/0.76	2.20/1.69	4.50/2.20	1.93/1.13
SCLE	Range	17–23/0–2	8–16/4–8	69–88/4–9	7–12/1–5
	Mean	21.0/0.4	12.6/6.6	76.8/6.0	8.8/2.8
	± SD	3.67/0.89	3.44/1.67	7.92/1.87	1.92/1.48

clinically normal skin and oral mucosa of healthy subjects [rev. in 1], were found in the lesional dermis, associated with CD_4^+ and CD_8^+ T cells, respectively. CD_{11c}^+ and CD_{14}^+ cells, presumable precursors to both CD_{1a}^+ and CD_{36}^+ DC, were found in perivascular location in the papillary dermis. By EM, cells with featus of Langerhans lineage, but without Birbeck granules, and dendritic macrophages, associated with lymphocytes and mast cells, were found in the lesional dermis. In addition, peculiar cells, dendritic in shape and rich in flat, rough cisternae, with moderately well developed Golgi apparatus and virtually no lysosomes, were found in the same location as the CD_{11c}^+ and CD_{14}^+ cells identified by light microscopy.

Discussion

Our results show that in cutaneous LE lesions the number and dendrite development of epidermal CD_{1a}^+ DC (i.e., Langerhans cells, (LC) are inversely related to the degree of histologically assessed epidermal atrophy, and are not reduced in nonatrophic areas. The previously claimed, overall reduction in the number of epidermal LC [5,6] may therefore be related to the average figure resulting from both atrophic and nonatrophic areas. The finding of epidermal CD_{11c}^+ and CD_{14}^+ cells restricted to atrophic areas suggests that the impairment of epidermal microenvironment, related to atrophy, does not allow the complete differentiation of these precursors into LC. Independent of their number, epidermal CD_{1a}^+ DC constantly show a reduced expression of HLA-DR antigen. These alterations in the cytological differentiation and/or expression of functionally meaningful molecules by epidermal LC in cutaneous LE lesions suggest an impairment of their immunological efficiency.

The constant finding of CD_{11c}^+, CD_{14}^+ cells with EM features of immature monocytoid cells around blood capillaries in the papillary dermis suggest that they possibly represent a single monocytic precursor to both CD_{1a}^+ and CD_{36}^+ DC, which seem to increase in number in a parallel fashion.

On the basis of our findings, we would like to propose the following steps in the pathogenesis of cutaneous LE lesions [7]: 1) a delayed-type, CD_4^+ T-cell/CD_{1a}^+ DC immune response occurs in the dermis and dermo-epidermal junction; 2) this response is possibly modulated by a suppressor CD_8^+ T cell circuit, in which CD_{36}^+ DC may act as accessory cells; 3) precursors to DC enter the dermis and presumably differentiate continuously into both CD_{1a}^+ and CD_{36}^+ DC within LE lesions; 4) the cell-mediated immune response starting from the dermis might be responsible for keratinocyte damage, leading to an alteration of the epidermal microenvironment; this alteration, in turn, would cause the observed impairment of LC difference within the epidermis.

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